



Sven-Eric Jordt, PhD
Associate Professor

Sairam V. Jabba, PhD
Senior Research Associate

*Duke University School of Medicine
Department of Anesthesiology
Durham NC 27710*

To:
Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852.

RE: Docket No. FDA-2017-N-4678

Modified Risk Tobacco Product Applications: Applications for Six Camel Snus Smokeless Tobacco Products
Submitted by R.J. Reynolds Tobacco Company

October 08, 2018

High levels of the synthetic sweetener sucralose in R.J. Reynolds Snus Products may increase the risk of youth tobacco initiation and consumption of sucralose exceeding the FDA-recommended Acceptable Daily Intake (ADI).

Dear Commissioner Gottlieb:

We are submitting this comment after reviewing the publicly available documents posted in conjunction with the TPSAC meeting on September 13-14, 2018, that discussed the MRTPAs submitted by R.J. Reynolds Tobacco Company for six Snus products. After reviewing the briefing documents by R.J. Reynolds and FDA and the recordings of the meeting, we are concerned that important facts about sweeteners in R.J. Reynolds Snus products were not discussed.

As a Professor in the Departments of Anesthesiology and Pharmacology and Cancer Biology at Duke University School of Medicine, I direct a research laboratory that investigates the effects of chemical irritants and natural products on the respiratory and nervous systems. Over the last 15 years the Jordt laboratory has made key discoveries related to the physiological and pharmacological effects of menthol, published in leading scientific journals such as Nature, the FASEB Journal and Tobacco Control (1-6). Moreover, I identified a key respiratory irritant receptor, the TRPA1 ion channel, a discovery for which I was awarded the Presidential Early Career Award for Scientists and Engineers (PECASE) by President Bush in 2007, among other honors.

Dr. Jabba, the co-author of this letter, is a Senior Research Associate in Jordt lab at Duke University and studies the toxicological and addiction properties of flavor chemicals in tobacco products. Drs. Jordt and Jabba are members of the Yale Center for the Study of Tobacco Product Use and Addiction (P50DA036151), one of the Tobacco Centers of Regulatory Science.

When reviewing the [FDA briefing document](#) for the TPSAC meeting, we noted the following statement on page 8, last paragraph:

“Ingredients added to the tobacco blend for the six Camel Snus products – such as sweetener, flavors, and humectant ingredients – are similar to those added to cigarettes. However, ingredient quantities vary between cigarettes and the six products due to the differences in product design and use.”

Based on our published scientific research and other information, we find that **ingredients added to Camel Snus products differ significantly from those added to cigarettes:**

1. Camel Snus products contain high levels of the synthetic high-intensity sweetener, sucralose

With this letter we include a research paper published in 2016 from our laboratory that describes the presence of high levels of the synthetic high-intensity sweetener, sucralose (Splenda), in R.J. Reynolds Snus products (5). Through chemical analysis we measured that the marketed R. J. Reynolds Camel Snus products, Camel mint and Camel mellow, contain between 6-7 mg sucralose per pouch (**Figure 1**), with each pouch added on average 1.12% or 1.26% (weight/weight) sucralose (Table 1) (5). A Tobacco Industry Documents search revealed a document from R.J. Reynolds listing similar amounts of sucralose in Camel mellow market testing products (7).

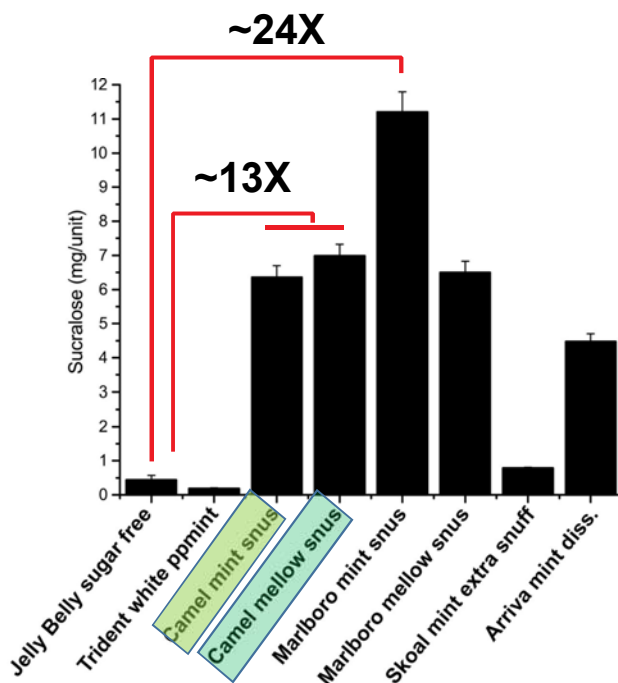


Figure 1: A Comparison of sucralose content in product units of confectionary products and snus. The Y-axis represents the average content of sucralose in mg per piece or pouch.

To our knowledge, **currently marketed cigarettes do not contain any sucralose**, or any other synthetic high intensity sweetener. Thus, **ingredients in Camel Snus products are significantly different from ingredients in cigarettes.**

2. Camel Snus products are much sweeter than other smokeless tobacco products

Sucralose is about 600 times sweeter than sugar. Thus, a Camel snus pouch, with 6-7mg of sucralose per pouch, is as sweet as 3.6g-4.2g of sugar. Since a Camel snus pouch weighs only 0.55g, **the sweetness of a Camel snus pouch is 6 – 8 fold more intense than the sweetness of a piece of sugar with the same weight.**

Camel snus products are also much sweeter than other currently marketed smokeless tobacco categories. In our published study we also analyzed sweetener content in pouched moist snuff, including Kodiak wintergreen, Kodiak mint, Skoal mint classic, Skoal mint Xtra and Skoal classic. We found that all pouched moist snuff products we analyzed contained saccharin, another synthetic high-intensity sweetener, but only at 0.0457-0.0895 % (weight/weight), more than 10-fold lower than the sucralose amounts we measured in Camel snus

products (5). Saccharin is 200-700-fold sweeter than sugar, similar to sucralose. Only one product, Skoal mint Xtra, contained additional sucralose, but again at much lower levels. **Thus, Camel snus products are much sweeter than widely used pouched moist snuff products.**

The sweetness of Camel snus products was only exceeded by another US-marketed snus product, Marlboro mint snus, suggesting that **the whole category of newly introduced US-marketed snus is intensely sweetened.**

3. Camel Snus products are sweeter than confectionary products

For comparison we also analyzed sugar-free confectionary products, found to contain sucralose, but also aspartame and bulking sugar alcohols (sorbitol, xylitol). The highest level of aspartame, 200-fold more sweet than sugar, was found in Ice Breakers, at 0.82% (weight/weight) (5). Sucralose contents were much lower. Thus, while some sugar-free confectionary products were intensely sweetened, Camel snus products are much sweeter.

4. Sucralose, the sweetener contained in Camel snus products, increases nicotine intake

Nicotine has a bitter taste and is irritating, eliciting a burning sensation in the mouth. We investigated the effect of sucralose on the oral aversion of adult mice to nicotine. The mice had never tasted nicotine or sweeteners before, modeling a naïve adult user. In a choice drinking behavioral assays (two bottle assay) we observed that sucralose diminished the aversive effects of oral nicotine in a dose dependent manner and increased the consumption of highly aversive nicotine solution (200 µg/mL) by ~3.5-fold (0.1% sucralose) 8.5-fold (1% sucralose). More importantly, naïve adolescent mice displayed a higher preference for sucralose-containing nicotine solution than adult mice, consuming more than 15 times of the sweetened over the unsweetened nicotine solution (**Figure 2**).

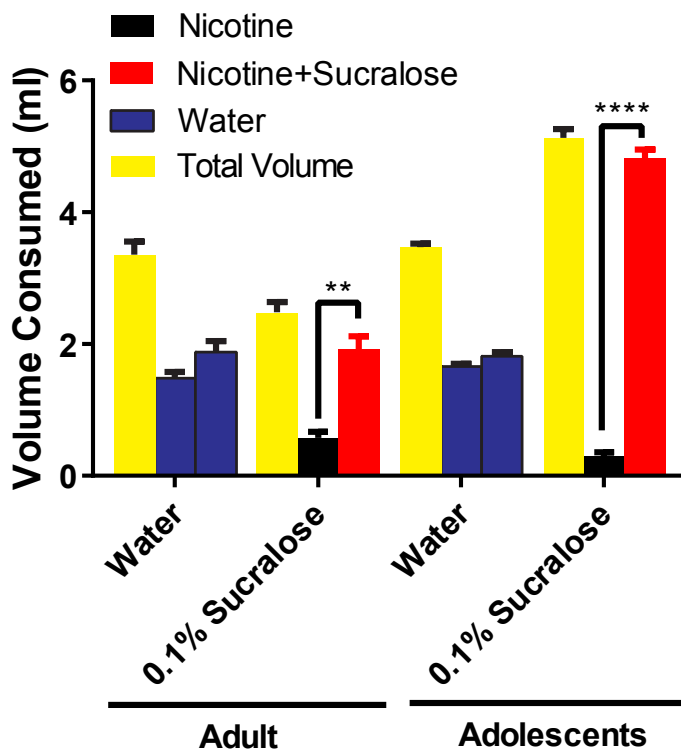


Figure 2: Influence of sucralose on nicotine aversion in a mouse-model by means of a two-two-bottle choice drinking assay. Adult and adolescent mice were present a choice to consume either nicotine (200 µg/mL) solution or nicotine solution mixed with 0.1% sucralose. Presence of sucralose reduced nicotine aversion, more robustly in adolescent mice.

Data is represented as mean ± s.e. where the mean is the average of volume consumed over a period of 4 nights; n=5-6 mice; ** is p<0.01; *** is p<0.001)

5. Sucralose promotes snus consumption

We next investigated whether the sucralose contained in snus determines snus product consumption and preference. Again, using mouse behavioral fluid consumption assays, we compared consumption of snus extracts between naïve wildtype mice and (naïve) mice lacking sweet perception. Sweet taste perception was eliminated by deletion of the gene encoding for the sweet taste receptor, *Tas1r2*, in taste buds of the mouse tongue. Compared to wildtype mice, we observed a significant (~25%) reduction in snus extract (Camel Mellow Snus) consumption in mice lacking sweet perception. Further analysis of snus extract consumption patterns suggested that the capability to perceive sucralose as sweet helped with overcoming the otherwise aversive taste of snus and initiate consumption (**Figure 3**).

These studies used mice since nicotine and tobacco product use initiation in never users, and especially in minors, cannot be studied ethically in human subjects. The nicotine concentrations in the snus extracts were around 150 µg/ml, a level estimated to be present in the mouth of users.

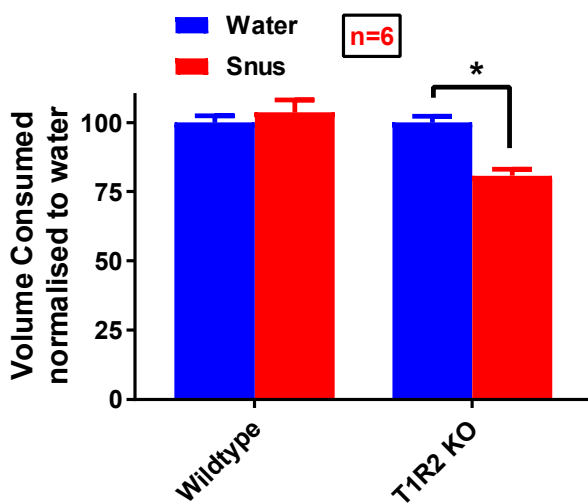


Figure 3: Influence of sweeteners on snus product consumption in adult wildtype and sweet perception deficient mice (*T1R2* knock out) using a one-bottle drinking assay. Adult mice were presented with a single bottle containing either water or Camel Mellow snus extract for four nights (extract diluted to contain nicotine @ 150 µg/mL and 0.017% sucralose). Sweet perception-deficient mice demonstrated an increased aversion to the snus product. In contrast wildtype mice showed no aversion to the snus product compared to water consumption. Data is represented as mean ± s.e. where the mean is the average of volume consumed over a period of 4 nights; n=6 mice; * is p<0.05)

Taken together, these results demonstrate that sucralose in Camel mellow snus suppresses the otherwise aversive and bitter taste of tobacco.

6. Consumption of Camel Snus products, together with other sucralose-sweetened products, may lead to sucralose intake exceeding the Acceptable Daily Intake (ADI) for this sweetener

The FDA has set limits for the maximal daily consumption of high intensity sweeteners.

<https://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm397725.htm>

The Acceptable Daily Intake (ADI) for sucralose is 5mg/kg bw/d. For a 60kg person the ADI is therefore 300 mg. Research by the tobacco industry revealed that the average male snus user consumes 12 pouches per day, sometimes more. With one snus pouch containing as much as 11mg of sucralose, the average user would consume 12/day x 11mg = 132 mg/day. While this amount is below the ADI, consumption of additional sucralose-containing products such as beverages, candy and baked goods, may lead users to exceed the ADI. For example, a can of diet soda (Pepsi One, Coke Zero, Diet Coke with Splenda, Diet Rite Cola) contains 38-68 mg sucralose, and sugar-free energy drinks may contain similar amounts. **Thus, the average snus user may exceed the ADI for sucralose when consuming a small number of servings of sucralose-containing soda or energy drinks.**

Implications and recommendations:

In summary, **the current findings suggest that R.J. Reynolds Camel snus products, and US-marketed snus products in general, are more highly sweetened than confectionary products, and any other currently marketed tobacco products.** With sucralose perceived as 600 times sweeter than sugar, the sweetness of R.J. Reynolds snus products by far exceeds the sweetness of their pouch weight in sugar.

Based on our finding, the ingredients in R.J. Reynold's snus products are significantly different from cigarettes. As a modified risk product, ***it is unclear why the R.J. Reynolds snus products are so intensely sweetened, whereas cigarettes, the product smokers are encouraged to switch from, are not.***

While the risk for developing cancer and other morbidities may be lower in snus users, ***we are concerned that the intense sweetness of R.J. Reynolds snus products may facilitate tobacco use initiation by youth and never smokers and thereby increase the number of tobacco users.***

The intense sweetness of R.J. Reynolds snus products may be desirable for never smokers since it masks the adverse taste and sensory effects of the processed tobacco that contains irritating and bitter nicotine and other tobacco constituents with aversive tastes. Children and adolescents strongly prefer sweetness and sweet flavors (8). Initiation of smokeless tobacco use often begins at a very young age, and the intense sweetness of Camel snus products may make it easier for youth to overcome the otherwise aversive bitter and irritating taste of tobacco (9). Our behavioral studies in mice clearly showed that sucralose reduced aversion to nicotine and snus product consumption.

Based on these findings and implications we recommend that:

- 1) **FDA requests information from R.J. Reynolds about sucralose content in all 6 products listed in this MRTPA.**
- 2) **R. J. Reynolds reveals the testing and decision making process resulting in the sucralose levels the company is adding to the marketed products.** Why are sucralose levels so much higher than in any other tobacco product, or in confectionary products?
- 3) **R.J. Reynolds submits information to FDA documenting that R.J. Reynolds performed an evaluation of the risk that availability of such highly sweetened products may increase the frequency of tobacco use initiation in youth and never users.**
- 4) **FDA acknowledges that R.J. Reynolds snus products have a significantly different composition of ingredients compared to cigarettes.** Addition of large amounts of a high-intensity sweetener such as sucralose, as measured in R.J. Reynolds snus products, fundamentally changes the taste properties of a product and consumer behavior related to the product. To our knowledge, currently marketed cigarettes do not contain sucralose, or any other synthetic high-intensity sweetener.

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Brief Report

High-Intensity Sweeteners in Alternative Tobacco Products

Shida Miao PhD¹, Evan S. Beach PhD^{1,2}, Toby J. Sommer PhD¹,
Julie B. Zimmerman PhD^{1,3}, Sven-Eric Jordt PhD^{2,4}

¹Department of Chemical and Environmental Engineering, Yale University, New Haven, CT; ²Yale Tobacco Center of Regulatory Science (TCORS), Department of Psychiatry, Yale School of Medicine, New Haven, CT; ³School of Forestry and Environmental Studies, Yale University, New Haven, CT; ⁴Department of Anesthesiology, Duke University School of Medicine, Durham, NC

Corresponding Author: Sven-Eric Jordt, PhD, Department of Anesthesiology, Duke University School of Medicine, Box 3094 MS27, Durham, NC 27710-3094, USA. Telephone: 919-681-4710; Fax : 919-684-2411; E-mail: sven.jordt@duke.edu

Abstract

Introduction: Sweeteners in tobacco products may influence use initiation and reinforcement, with special appeal to adolescents. Recent analytical studies of smokeless tobacco products (snuff, snus, dissolvables) detected flavorants identical to those added to confectionary products such as hard candy and chewing gum. However, these studies did not determine the levels of sweeteners. The objective of the present study was to quantify added sweeteners in smokeless tobacco products, a dissolvable product, electronic cigarette liquids and to compare with sweetener levels in confectionary products.

Methods: Sweetener content of US-sourced smokeless tobacco, electronic cigarette liquid, and confectionary product samples was analyzed by liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS).

Results: All smokeless products contained synthetic high intensity sweeteners, with snus and dissolvables exceeding levels in confectionary products (as much as 25-fold). All snus samples contained sucralose and most also aspartame, but no saccharin. In contrast, all moist snuff samples contained saccharin. The dissolvable sample contained sucralose and sorbitol. Ethyl maltol was the most common sweet-associated component in electronic cigarette liquids.

Discussion: Sweetener content was dependent on product category, with saccharin in moist snuff, an older category, sucralose added at high levels to more recently introduced products (snus, dissolvable) and ethyl maltol in electronic cigarette liquid. The very high sweetener concentrations may be necessary for the consumer to tolerate the otherwise aversive flavors of tobacco ingredients. Regulation of sweetener levels in smokeless tobacco products may be an effective measure to modify product attractiveness, initiation and use patterns.

Implications: Dissolvables, snus and electronic cigarettes have been promoted as risk-mitigation products due to their relatively low content of nitrosamines and other tobacco toxicants. This study is the first to quantify high intensity sweeteners in snus and dissolvable products. Snus and dissolvables contain the high intensity sweetener, sucralose, at levels higher than in confectionary products. The high sweetness of alternative tobacco products makes these products attractive to adolescents. Regulation of sweetener content in non-cigarette products is suggested as an efficient means to control product palatability and to reduce initiation in adolescents.

Introduction

In the United States, the Family Smoking Prevention and Tobacco Control Act (FSPTCA) restricts the sales of flavored cigarettes, with the exemption of menthol cigarettes. These restrictions do not apply to smokeless tobacco products, cigars, and electronic cigarettes. These products are available in a wide range of flavors with novel flavor combinations introduced almost daily. The presence of characterizing flavor additives is expected to attract both smokers and non-smokers, and especially adolescents.¹⁻³ Previous studies have noted similarities in the content of flavor chemicals in tobacco products and confectionary products such as hard candy, mints, and chewing gum.^{4,5} Tobacco flavorants include many of the esters, alcohols, terpenes, and aromatic chemicals added to foods. For example, benzyl alcohol is used as a flavoring both in cherry candies and cherry-flavored tobacco products.⁵ Electronic cigarette liquids also contain a wide range of known flavor chemicals used in the food industry.⁶

In contrast to these aroma flavorings, only limited information is available about the presence of sweeteners in the currently marketed smokeless tobacco products and electronic cigarette liquids. Traditionally, chewing tobacco and moist snuff have been sweetened either with table sugar (sucrose), causing documented oral health problems in users, or with saccharin.^{7,8} Tobacco Industry Documents list sweetener contents in some products, however, this information is likely outdated and new sweeteners and product categories have been introduced.^{9,10} For currently marketed products manufacturers list sweeteners as ingredients, including saccharin and sucralose, high intensity sweeteners several hundred times sweeter than sucrose.¹⁰⁻¹⁶ The quantities and types of sweeteners contained in individual products, and how these compare to confectionary products, are unknown.

Sweeteners have powerful psychophysical effects and are known to mask the unpleasant taste of tobacco constituents and reduce oral aversion to nicotine in animals.^{17,18} Analogous to candies and sweetened beverages designed to appeal to teenagers and young adults, addition of sweeteners to tobacco products might promote product uptake and determine preference and use patterns.^{19,20}

In the present study, 18 tobacco products, including snus, moist snuff, dissolvable tobacco, and electronic cigarette liquids marketed in the United States were analyzed by liquid chromatography–mass spectrometry [LC-MS], to determine levels of natural and high-intensity sweeteners. Sweetener contents in representative confectionary products and soda were analyzed and compared.

Methods

Product Samples

Sixteen tobacco products were purchased from stores in the New Haven, CT, area including four snus products, five moist snuffs, five electronic cigarette cartridges, and two electronic cigarette refill liquids. One electronic refill liquid was purchased online from the manufacturer (V2), and one dissolvable tobacco product was procured from an out of state online vendor. For comparison with other high-intensity sweetened products, four sugar-free confectionary products of different brands and two sugar-free beverages of different brands were bought from area stores (Supplementary Table 1).

Chemical Analysis

Levels of synthetic high-intensity sweeteners (sucralose, cyclamates, saccharin, aspartame, acesulfame potassium), bio-derived

high-intensity sweeteners (stevioside, glycyrrhizin), sugar alcohols, natural sugars, and other constituents were determined by a modified LC-MS method previously used in our laboratory for the analysis of sweetener content in environmental samples²¹ (Supplementary Methods). This technique provides a conservative estimate of sweetener levels; in some samples the tobacco matrix may cause minor suppression of MS response.²²

Results

All tested products contained no or only very small amounts of the sugars, glucose (<0.072 % w/w) or sucrose (<0.024 % w/w). As expected, the high-intensity sweeteners, sucralose, or aspartame, were detected in the soda and confectionary products (Table 1). The bulk of all mint lozenge products consisted of the sugar alcohol, sorbitol. Sucralose was detected in all snus products at high levels, with three of the four snus products also containing aspartame (Table 1). Saccharin was only detected in the moist snuff products. Snuff products contained no aspartame and only one contained a comparably small amount of sucralose (Skool mint Xtra). No high-intensity sweeteners were detected in the electronic cigarette liquids tested (Table 1). Two of the liquids contained traces of sorbitol (<0.003 % w/w). Ethyl maltol was detected in six of the eight liquids. All the E-liquids had glycerol as carrier, three of them also contained propylene glycol (Supplementary Table 2). The dissolvable product consisted of a large percentage (59.0 ± 3.0 % w/w) of sorbitol, and contained a high amount of sucralose, but no aspartame or saccharin (Table 1).

The average total amount of sucralose per product unit (piece, lozenge, or strip) was calculated for the sucralose-containing confectionary and smokeless tobacco products (Figure 1). Amounts of sucralose per unit were much higher in the snus products (>6 mg/unit, one product > 11 mg/unit) than in the confectionary products (<0.4 mg/unit). The single snuff product containing sucralose had <1 mg/unit. Sucralose content in the dissolvable product was higher (4.48 mg/unit).

Among the nine snus and moist snuff products, seven were in the form of small pouches. The content of sweeteners in the pouch material, comprising about 10% of total product weight, followed distributions in the bulk products, but concentrations were all lower (Supplementary Tables 3–5).

Discussion

In the present study, all the tested snus and moist snuff products contained high-intensity sweeteners. All tested moist snuff products contained saccharin as the sole added synthetic sweetener with one exception containing roughly equal amounts of both saccharin and sucralose. Manufacturers have been adding saccharin to smokeless tobacco products since 1891, when R. J. Reynolds introduced saccharin-sweetened chewing tobacco.⁷ In fact, the tobacco industry was the first to license synthetic high-intensity sweeteners to add to consumer products, likely to improve shelf stability, product uniformity and create brand identity.⁷ The majority of the moist snuff products investigated here were brought to market prior to introduction of sucralose in 1999.¹⁰ Saccharin, in addition to being perceived as sweet, has a bitter taste, a property not shared by sucralose and aspartame that have replaced saccharin in most high-intensity sweetened food products.³ It is possible that tobacco manufacturers did not replace saccharin in snuff products because long term users have

Table 1. Sweetener Levels in Alternative Tobacco Products, Soda, and Confectionary Products

Category	Product	Sorbitol	Aspartame	Saccharin	Sucralose	Ethyl maltol
Soda	Cherry Limeade				0.0145 ± 0.0022	
	Waist Watcher diet				0.0143 ± 0.0023	
Candy	Jelly Belly sugar free	0.0388 ± 0.0004			0.0369 ± 0.0113	
Mint lozenge	Life Savers sugar free	85.3 ± 0.8	0.270 ± 0.003			
	Ice Breakers sugar free	96.7 ± 0.71	0.820 ± 0.002			
	Altoids smalls peppermint	38.9 ± 1.18			0.023 ± 0.006	
Gum	Trident white peppermint	0.375 ± 0.016	0.132 ± 0.004		0.0132 ± 0.0014	
Snus	Camel mint	<0.001	0.00932 ± 0.00021		1.12 ± 0.06	
	Camel mellow		0.0128 ± 0.0002		1.26 ± 0.06	
	Marlboro mint				1.32 ± 0.07	
	Marlboro mellow		0.00759 ± 0.00080		0.690 ± 0.035	
Moist snuff	Kodiak mint			0.0895 ± 0.0131		
	Kodiak wintergreen			0.0457 ± 0.0006		
	Skoal mint classic			0.0563 ± 0.0030		
	Skoal mint – Xtra			0.0593 ± 0.0033	0.0519 ± 0.0010	
E-cigarette	Skoal classic straight			0.0587 ± 0.0042		
	Blu classic tobacco	<0.003				<0.0003
	Blu magnificent menthol	<0.0005				0.00133 ± 0.00005
	Blu vanilla					0.00908 ± 0.00045
	Finito rich tobacco					
	Finito cool menthol					0.00311 ± 0.0016
	CT menthol					0.00338 ± 0.00017
	CT packed					0.0890 ± 0.001
	V2 red					
Dissolvable	Arriva	59.0 ± 3.0			1.79 ± 0.09	

Data are stated as % w/w of product unit as received; means from three samples each, with standard error; blank fields indicate nondetected (n.d.)

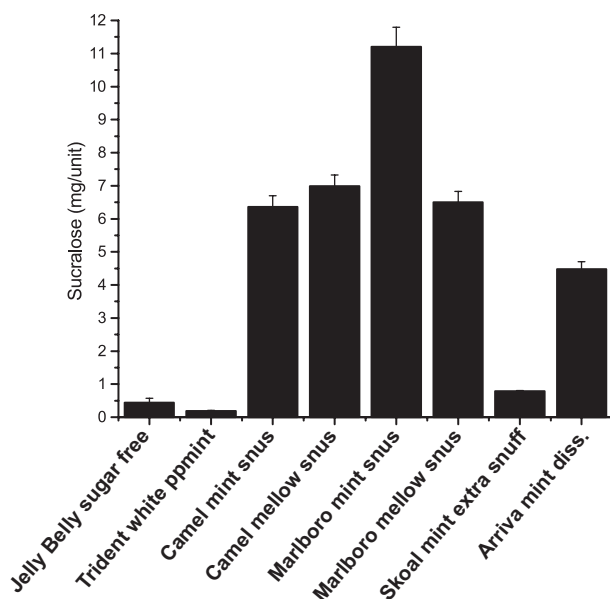


Figure 1. Comparison of sucralose content in product units of confectionary products and snus. Average content of sucralose in mg per piece or pouch is displayed. Data derived from Table 1.

been habituated to its taste profile and would disapprove of a change to other sweeteners. This view is also supported by the observation that saccharin content in the currently marketed products analyzed here did not differ much from levels determined in snuff products more than 20 years ago.⁹ The lower price of saccharin compared to sucralose may also explain its continued use in the product category.

In contrast, all four snus products tested here contained sucralose, most in combination with aspartame. Snus products were introduced to the US market in 2006 when sucralose was already widely used in food products.²³ Sucralose content in the tested snus products, both % w/w and weight per product unit, exceeded the levels in any of the other solid confectionary products (candy, mint lozenges, chewing gum). The absolute amounts of sucralose in snus were 14- to 25-fold higher than the highest content found in a candy product. The bulk of some of the confectionary products consisted of a high percentage of sorbitol, a sugar alcohol with a sweetness lower than table sugar (sucrose). Together with sorbitol, smaller amounts of sucralose and aspartame are likely sufficient for these products to reach the desired level of sweetness. Intriguingly, the dissolvable tobacco product tested here also contained substantial amounts of sorbitol with sucralose added at an amount approaching that found in the snus products.

Six of the eight E-cigarette liquids contained ethyl maltol, known to be a sweet taste potentiator and previously reported in E-liquids.^{5,6,24} Propylene glycol and glycerol, the major constituents of the E-liquids tested, are lightly sweet. Their sweetness may be enhanced by ethyl maltol and other popular sweet-associated flavorings.^{25,26} Ethyl maltol was awarded GRAS status (Generally Recognized As Safe) from the Flavor & Extracts Manufacturers Association (FEMA) for the intended use as a food additive. Some E-liquids vendors advertise the GRAS label as supportive of safety for the flavorants added to their products. However, FEMA has repudiated these claims since GRAS status only applies to use in food and not in E-cigarettes for inhalational delivery.²⁷ It is unknown whether ethyl maltol is chemically stable in E-liquids, and when these are heated and vaporized.

High-intensity sweeteners were not detected in the E-liquids tested suggesting that the major manufacturers of E-cigarettes and E-liquids do not include high-intensity sweeteners in their E-liquid formulations. However, online vendors currently offer sucralose liquids for sale to customers to mix with their E-liquids. While sucralose is an FDA-approved food additive, its health effects and metabolic fate when delivered by E-cigarette are unknown.

In summary, the current findings suggest that US-marketed new smokeless tobacco products, snus and dissolvables, are more highly sweetened than confectionary products. With sucralose perceived as 600 times sweeter than sugar, and added aspartame, the sweetness of snus and dissolvable products exceed the sweetness of their unit (pouch or lozenge) weight in sugar. Optimal sweetener levels were likely determined in tests by company-internal panelists and consumer groups, suggesting that higher levels of sweetness are required to establish palatability and liking of these tobacco-containing products. The intense sweetness may be necessary to mask the adverse taste and sensory effects of the processed tobacco that contains irritating and bitter nicotine and other tobacco constituents with adverse tastes. Sweeteners are known to suppress the perception of bitter taste and to inhibit the sensation of irritation.²⁸ While sucralose uptake from snus alone is unlikely to exceed the FDA-determined acceptable daily intake (ADI), daily repeated use of snus together with consumption of other sucralose-sweetened products such as soda, sweetener packets and food products may lead to continuous high exposure. Recent studies revealed that high-intensity sweeteners affected metabolic signaling in pancreatic beta cells and changed the composition of the gut microbiome, potentially contributing to metabolic dysregulation.²⁹

Dissolvables and snus have been promoted as risk-mitigation products due to their relatively low content of nitrosamines and other tobacco toxicants. While not as popular, these products may increase the risk of polytobacco use and their intense sweetness is of concern since it may appeal especially to adolescents who initiate tobacco product use.^{30,31} In addition to E-cigarettes, other sweet flavored tobacco products such as small cigars have made rapid inroads among adolescent populations and remain unregulated.^{32,33} Among the wide variety of flavors offered intense sweetness appears to be a common denominator in the majority of the newly introduced products. Thus, the regulation of sweetener content may represent an efficient means to control palatability of a wide range of products and to reduce tobacco product use initiation.

Supplementary Material

Supplementary Tables 1 to 5 and Supplementary Methods can be found online at <http://www.ntr.oxfordjournals.org>

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Declaration of Interests

The authors declare no competing interests.

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